

# EXHIBIT D

## (PART 3 OF 3)

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sensor control unit 44 for contacting the contact pads 49 on the sensor 42. Each pin 84 also has a proximal end that is coupled to a wire or other conductive strip that is, in turn, coupled to the rest of the electronic components (e.g., the voltage source 95 and measurement circuit 96 of FIGS. 18A and 18B) within the on-skin sensor control unit 44. Alternatively, the pins 84 may be coupled directly to the rest of the electronics.

In another embodiment, the conductive contacts 80 are formed as a series of conducting regions 88 with interspersed insulating regions 90, as illustrated in FIG. 19B. The conducting regions 88 may be as large or larger than the contact pads 49 on the sensor 42 to alleviate registration concerns. However, the insulating regions 90 should have sufficient width so that a single conductive region 88 does not overlap with two contact pads 49 as determined based on the expected variation in the position of the sensor 42 and contact pads 49 with respect to the conductive contacts 80. The conducting regions 88 are formed using materials such as metals, alloys, or conductive carbon. The insulating regions 90 may be formed using known insulating materials including, for example, insulating plastic or polymer materials.

In a further embodiment, a unidirectional conducting adhesive 92 may be used between the contact pads 49 on the sensor 42 and conductive contacts 80 implanted or otherwise formed in the on-skin sensor control unit 44, as shown in FIG. 19C.

In yet another embodiment, the conductive contacts 80 are conductive members 94 that extend from a surface of the on-skin sensor control unit 44 to contact the contact pads 49, as shown in FIG. 19D. A variety of different shapes may be used for these members, however, they should be electrically insulated from each other. The conductive members 94 may be made using metal, alloy, conductive carbon, or conducting plastics and polymers.

Any of the exemplary conductive contacts 80 described above may extend from either the upper surface of the interior of the on-skin sensor control unit 44, as illustrated in FIGS. 19A–19C, or from the lower surface of the interior of the on-skin sensor control unit 44, as illustrated in FIG. 19D, or from both the upper and lower surfaces of the interior of the on-skin sensor control unit 44, particularly when the sensor 42 has contact pads 49 on both sides of the sensor.

Conductive contacts 80 on the exterior of the housing 45 may also have a variety of shapes as indicated in FIGS. 19E and 19F. For example, the conductive contacts 80 may be embedded in (FIG. 19E) or extending out of (FIG. 19F) the housing 45.

The conductive contacts 80 are preferably made using a material which will not corrode due to contact with the contact pads 49 of the sensor 42. Corrosion may occur when two different metals are brought in contact. Thus, if the contact pads 49 are formed using carbon then the preferred conductive contacts 80 may be made using any material, including metals or alloys. However, if any of the contact pads 49 are made with a metal or alloy then the preferred conductive contacts 80 for coupling with the metallic contact pads are made using a non-metallic conductive material, such as conductive carbon or a conductive polymer, or the conductive contacts 80 and the contact pads 49 are separated by a non-metallic material, such as a unidirectional conductive adhesive.

In one embodiment, electrical contacts are eliminated between the sensor 42 and the on-skin sensor control unit 44. Power is transmitted to the sensor via inductive coupling,

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using, for example, closely space antennas (e.g., facing coils) (not shown) on the sensor and the on-skin sensor control unit. Changes in the electrical characteristics of the sensor control unit 44 (e.g., current) induce a changing magnetic field in the proximity of the antenna. The changing magnetic field induces a current in the antenna of the sensor. The close proximity of the sensor and on-skin sensor control unit results in reasonably efficient power transmission. The induced current in the sensor may be used to power potentiostats, operational amplifiers, capacitors, integrated circuits, transmitters, and other electronic components built into the sensor structure. Data is transmitted back to the sensor control unit, using, for example, inductive coupling via the same or different antennas and/or transmission of the signal via a transmitter on the sensor. The use of inductive coupling can eliminate electrical contacts between the sensor and the on-skin sensor control unit. Such contacts are commonly a source of noise and failure. Moreover, the sensor control unit may then be entirely sealed which may increase the waterproofing of the on-skin sensor control unit.

An exemplary on-skin sensor control unit 44 can be prepared and used in the following manner. A mounting unit 77 having adhesive on the bottom is applied to the skin. An insertion gun 200 (see FIG. 26) carrying the sensor 42 and the insertion device 120 is positioned against the mounting unit 77. The insertion gun 200 and mounting unit 77 are optionally designed such that there is only one position in which the two properly mate. The insertion gun 200 is activated and a portion of the sensor 42 and optionally a portion of the insertion device 120 are driven through the skin into, for example, the subcutaneous tissue. The insertion gun 200 withdraws the insertion device 200, leaving the portion of the sensor 42 inserted through the skin. The housing 45 of the on-skin control unit 44 is then coupled to the mounting unit 77. Optionally, the housing 45 and the mounting unit 77 are formed such that there is only one position in which the two properly mate. The mating of the housing 45 and the mounting unit 77 establishes contact between the contact pads 49 (see e.g., FIG. 2) on the sensor 42 and the conductive contacts 80 on the on-skin sensor control unit 44. Optionally, this action activates the on-skin sensor control unit 44 to begin operation.

#### On-Skin Control Unit Electronics

The on-skin sensor control unit 44 also typically includes at least a portion of the electronic components that operate the sensor 42 and the analyte monitoring device system 40. One embodiment of the electronics in the on-skin control unit 44 is illustrated as a block diagram in FIG. 18A. The electronic components of the on-skin sensor control unit 44 typically include a power supply 95 for operating the on-skin control unit 44 and the sensor 42, a sensor circuit 97 for obtaining signals from and operating the sensor 42, a measurement circuit 96 that converts sensor signals to a desired format, and a processing circuit 109 that, at minimum, obtains signals from the sensor circuit 97 and/or measurement circuit 96 and provides the signals to an optional transmitter 98. In some embodiments, the processing circuit 109 may also partially or completely evaluate the signals from the sensor 42 and convey the resulting data to the optional transmitter 98 and/or activate an optional alarm system 94 (see FIG. 18B) if the analyte level exceeds a threshold. The processing circuit 109 often includes digital logic circuitry.

The on-skin sensor control unit 44 may optionally contain a transmitter 98 for transmitting the sensor signals or processed data from the processing circuit 109 to a receiver/display unit 46, 48; a data storage unit 102 for temporarily

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or permanently storing data from the processing circuit 109; a temperature probe circuit 99 for receiving signals from and operating a temperature probe 66; a reference voltage generator 101 for providing a reference voltage for comparison with sensor-generated signals; and/or a watchdog circuit 103 that monitors the operation of the electronic components in the on-skin sensor control unit 44.

Moreover, the sensor control unit 44 often includes digital and/or analog components utilizing semiconductor devices, such as transistors. To operate these semiconductor devices, the on-skin control unit 44 may include other components including, for example, a bias control generator 105 to correctly bias analog and digital semiconductor devices, an oscillator 107 to provide a clock signal, and a digital logic and timing component 109 to provide timing signals and logic operations for the digital components of the circuit.

As an example of the operation of these components, the sensor circuit 97 and the optional temperature probe circuit 99 provide raw signals from the sensor 42 to the measurement circuit 96. The measurement circuit 96 converts the raw signals to a desired format, using for example, a current-to-voltage converter, current-to-frequency converter, and/or a binary counter or other indicator that produces a signal proportional to the absolute value of the raw signal. This may be used, for example, to convert the raw signal to a format that can be used by digital logic circuits. The processing circuit 109 may then, optionally, evaluate the data and provide commands to operate the electronics.

FIG. 18B illustrates a block diagram of another exemplary on-skin control unit 44 that also includes optional components such as a receiver 99 to receive, for example, calibration data; a calibration storage unit 100 to hold, for example, factory-set calibration data, calibration data obtained via the receiver 99 and/or operational signals received, for example, from a receiver/display unit 46, 48 or other external device; an alarm system 104 for warning the patient; and a deactivation switch 111 to turn off the alarm system.

Functions of the analyte monitoring system 40 and the sensor control unit 44 may be implemented using either software routines, hardware components, or combinations thereof. The hardware components may be implemented using a variety of technologies, including, for example, integrated circuits or discrete electronic components. The use of integrated circuits typically reduces the size of the electronics, which in turn may result in a smaller on-skin sensor control unit 44.

The electronics in the on-skin sensor control unit 44 and the sensor 42 are operated using a power supply 95. One example of a suitable power supply 95 is a battery, for example, a thin circular battery, such as those used in many watches, hearing aids, and other small electronic devices. Preferably, the battery has a lifetime of at least 30 days, more preferably, a lifetime of at least three months, and most preferably, a lifetime of at least one year. The battery is often one of the largest components in the on-skin control unit 44, so it is often desirable to minimize the size of the battery. For example, a preferred battery's thickness is 0.5 mm or less, preferably 0.35 mm or less, and most preferably 0.2 mm or less. Although multiple batteries may be used, it is typically preferred to use only one battery.

The sensor circuit 97 is coupled via the conductive contacts 80 of the sensor control unit 44 to one or more sensors 42, 42'. Each of the sensors represents, at minimum, a working electrode 58, a counter electrode 60 (or counter/reference electrode), and an optional reference electrode 62.

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When two or more sensors 42, 42' are used, the sensors typically have individual working electrodes 58, but may share a counter electrode 60, counter/reference electrode, and/or reference electrode 52.

The sensor circuit 97 receives signals from and operates the sensor 42 or sensors 42, 42'. The sensor circuit 97 may obtain signals from the sensor 42 using amperometric, coulometric, potentiometric, voltammetric, and/or other electrochemical techniques. The sensor circuit 97 is exemplified herein as obtaining amperometric signals from the sensor 42, however, it will be understood that the sensor circuit can be appropriately configured for obtaining signals using other electrochemical techniques. To obtain amperometric measurements, the sensor circuit 97 typically includes a potentiostat that provides a constant potential to the sensor 42. In other embodiments, the sensor circuit 97 includes an amperostat that supplies a constant current to the sensor 42 and can be used to obtain coulometric or potentiometric measurements.

The signal from the sensor 42 generally has at least one characteristic, such as, for example, current, voltage, or frequency, which varies with the concentration of the analyte. For example, if the sensor circuit 97 operates using amperometry, then the signal current varies with analyte concentration. The measurement circuit 96 may include circuitry which converts the information-carrying portion of the signal from one characteristic to another. For example, the measurement circuit 96 may include a current-to-voltage or current-to-frequency converter. The purpose of this conversion may be to provide a signal that is, for example, more easily transmitted, readable by digital circuits, and/or less susceptible to noise contributions.

One example of a standard current-to-voltage converter is provided in FIG. 20A. In this converter, the signal from the sensor 42 is provided at one input terminal 134 of an operational amplifier 130 ("op amp") and coupled through a resistor 138 to an output terminal 136. This particular current-to-voltage converter 131 may, however, be difficult to implement in a small CMOS chip because resistors are often difficult to implement on an integrated circuit. Typically, discrete resistor components are used. However, the use of discrete components increases the space needed for the circuitry.

An alternative current-to-voltage converter 141 is illustrated in FIG. 20B. This converter includes an op amp 140 with the signal from the sensor 42 provided at input terminal 144 and a reference potential provided at input terminal 142. A capacitor 145 is placed between the input terminal 144 and the output terminal 146. In addition, switches 147a, 147b, 149a, and 149b are provided to allow the capacitor to charge and discharge at a rate determined by a clock (CLK) frequency. In operation, during one half cycle, switches 147a and 147b close and switches 149a and 149b open allowing the capacitor 145 to charge due to the attached potential V1. During the other half cycle, switches 147a and 147b open and switches 149a and 149b close to ground and allow the capacitor 145 to partially or fully discharge. The reactive impedance of the capacitor 145 is analogous to the resistance of the resistor 138 (see FIG. 20A), allowing the capacitor 145 to emulate a resistor. The value of this "resistor" depends on the capacitance of the capacitor 145 and the clock frequency. By altering the clock frequency, the reactive impedance ("resistance value") of the capacitor changes. The value of the impedance ("resistance") of the capacitor 145 may be altered by changing the clock frequency. Switches 147a, 147b, 149a, and 149b may be implemented in a CMOS chip using, for example, transistors.

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A current-to-frequency converter may also be used in the measurement circuit 96. One suitable current-to-frequency converter includes charging a capacitor using the signal from the sensor 42. When the potential across the capacitor exceeds a threshold value, the capacitor is allowed to discharge. Thus, the larger the current from the sensor 42, the quicker the threshold potential is achieved. This results in a signal across the capacitor that has an alternating characteristic, corresponding to the charging and discharging of the capacitor, having a frequency which increases with an increase in current from the sensor 42.

In some embodiments, the analyte monitoring system 40 includes two or more working electrodes 58 distributed over one or more sensors 42. These working electrodes 58 may be used for quality control purposes. For example, the output signals and/or analyzed data derived using the two or more working electrodes 58 may be compared to determine if the signals from the working electrodes agree within a desired level of tolerance. If the output signals do not agree, then the patient may be alerted to replace the sensor or sensors. In some embodiments, the patient is alerted only if the lack of agreement between the two sensors persists for a predetermined period of time. The comparison of the two signals may be made for each measurement or at regular intervals. Alternatively or additionally, the comparison may be initiated by the patient, or another person. Moreover, the signals from both sensors may be used to generate data or one signal may be discarded after the comparison.

Alternatively, if, for example, two working electrodes 58 have a common counter electrode 60 and the analyte concentration is measured by amperometry, then the current at the counter electrode 60 should be twice the current at each of the working electrodes, within a predetermined tolerance level, if the working electrodes are operating properly. If not, then the sensor or sensors should be replaced, as described above.

An example of using signals from only one working electrode for quality control includes comparing consecutive readings obtained using the single working electrode to determine if they differ by more than a threshold level. If the difference is greater than the threshold level for one reading or over a period of time or for a predetermined number of readings within a period of time then the patient is alerted to replace the sensor 42. Typically, the consecutive readings and/or the threshold level are determined such that all expected excursions of the sensor signal are within the desired parameters (i.e., the sensor control unit 44 does not consider true changes in analyte concentration to be a sensor failure).

The sensor control unit 44 may also optionally include a temperature probe circuit 99. The temperature probe circuit 99 provides a constant current through (or constant potential) across the temperature probe 66. The resulting potential (or current) varies according to the resistance of the temperature dependent element 72.

The output from the sensor circuit 97 and optional temperature probe circuit is coupled into a measurement circuit 96 that obtains signals from the sensor circuit 97 and optional temperature probe circuit 99 and, at least in some embodiments, provides output data in a form that, for example can be read by digital circuits. The signals from the measurement circuit 96 are sent to the processing circuit 109, which in turn may provide data to an optional transmitter 98. The processing circuit 109 may have one or more of the following functions: 1) transfer the signals from the measurement circuit 96 to the transmitter 98, 2) transfer signals from the measurement circuit 96 to the data storage

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circuit 102, 3) convert the information-carrying characteristic of the signals from one characteristic to another (when, for example, that has not been done by the measurement circuit 96), using, for example, a current-to-voltage converter, a current-to-frequency converter, or a voltage-to-current converter, 4) modify the signals from the sensor circuit 97 using calibration data and/or output from the temperature probe circuit 99, 5) determine a level of an analyte in the interstitial fluid, 6) determine a level of an analyte in the bloodstream based on the sensor signals obtained from interstitial fluid, 7) determine if the level, rate of change, and/or acceleration in the rate of change of the analyte exceeds or meets one or more threshold values, 8) activate an alarm if a threshold value is met or exceeded, 9) evaluate trends in the level of an analyte based on a series of sensor signals, 10) determine a dose of a medication, and 11) reduce noise and/or errors, for example, through signal averaging or comparing readings from multiple working electrodes 58.

The processing circuit 109 may be simple and perform only one or a small number of these functions or the processing circuit 109 may be more sophisticated and perform all or most of these functions. The size of the on-skin sensor control unit 44 may increase with the increasing number of functions and complexity of those functions that the processing circuit 109 performs. Many of these functions may not be performed by a processing circuit 109 in the on-skin sensor control unit 44, but may be performed by another analyzer 152 in the receiver/display units 46, 48 (see FIG. 22).

One embodiment of the measurement circuit 96 and/or processing circuit 109 provides as output data, the current flowing between the working electrode 58 and the counter electrode 60. The measurement circuit 96 and/or processing circuit 109 may also provide as output data a signal from the optional temperature probe 66 which indicates the temperature of the sensor 42. This signal from the temperature probe 66 may be as simple as a current through the temperature probe 66 or the processing circuit 109 may include a device that determines a resistance of the temperature probe 66 from the signal obtained from the measurement circuit 96 for correlation with the temperature of the sensor 42. The output data may then be sent to a transmitter 98 that then transmits this data to at least one receiver/display device 46, 48.

Returning to the processing circuit 109, in some embodiments processing circuit 109 is more sophisticated and is capable of determining the analyte concentration or some measure representative of the analyte concentration, such as a current or voltage value. The processing circuit 109 may incorporate the signal of the temperature probe to make a temperature correction in the signal or analyzed data from the working electrode 58. This may include, for example, scaling the temperature probe measurement and adding or subtracting the scaled measurement to the signal or analyzed data from the working electrode 58. The processing circuit 109 may also incorporate calibration data which has been received from an external source or has been incorporated into the processing circuit 109, both of which are described below, to correct the signal or analyzed data from the working electrode 58. Additionally, the processing circuit 109 may include a correction algorithm for converting interstitial analyte level to blood analyte level. The conversion of interstitial analyte level to blood analyte level is described, for example, in Schmidtke, et al., "Measurement and Modeling of the Transient Difference Between Blood and Subcutaneous Glucose Concentrations in the Rat after



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Injection of Insulin", Proc. of the Nat'l Acad. of Science. 95, 294-299 (1998) and Quinn, et al., "Kinetics of Glucose Delivery to Subcutaneous Tissue in Rats Measured with 0.3 mm Amperometric Microsensors", Am. J. Physiol., 269 (Endocrinol. Metab. 32), E155-E161 (1995), incorporated herein by reference.

In some embodiments, the data from the processing circuit 109 is analyzed and directed to an alarm system 94 (see FIG. 18B) to warn the user. In at least some of these embodiments, a transmitter is not used as the sensor control unit performs all of the needed functions including analyzing the data and warning the patient.

However, in many embodiments, the data (e.g., a current signal, a converted voltage or frequency signal, or fully or partially analyzed data) from processing circuit 109 is transmitted to one or more receiver/display units 46, 48 using a transmitter 98 in the on-skin sensor control unit 44. The transmitter has an antenna 93, such as a wire or similar conductor, formed in the housing 45. The transmitter 98 is typically designed to transmit a signal up to about 2 meters or more, preferably up to about 5 meters or more, and more preferably up to about 10 meters or more, when transmitting to a small receiver/display unit 46, such as a palm-size, belt-worn receiver. The effective range is longer when transmitting to a unit with a better antenna, such as a bedside receiver. As described in detail below, suitable examples of receiver/display units 46, 48 include units that can be easily worn or carried or units that can be placed conveniently on, for example, a nightstand when the patient is sleeping.

The transmitter 98 may send a variety of different signals to the receiver/display units 46, 48, typically, depending on the sophistication of the processing circuit 109. For example, the processing circuit 109 may simply provide raw signals, for example, currents from the working electrodes 58, without any corrections for temperature or calibration, or the processing circuit 109 may provide converted signals which are obtained, for example, using a current-to-voltage converter 131 or 141 or a current-to-frequency converter. The raw measurements or converted signals may then be processed by an analyzer 152 (see FIG. 22) in the receiver/display units 46, 48 to determine the level of an analyte, optionally using temperature and calibration corrections. In another embodiment, the processing circuit 109 corrects the raw measurements using, for example, temperature and/or calibration information and then the transmitter 98 sends the corrected signal, and optionally, the temperature and/or calibration information, to the receiver/display units 46, 48. In yet another embodiment, the processing circuit 109 calculates the analyte level in the interstitial fluid and/or in the blood (based on the interstitial fluid level) and transmits that information to the one or more receiver/display units 46, 48, optionally with any of the raw data and/or calibration or temperature information. In a further embodiment, the processing circuit 109 calculates the analyte concentration, but the transmitter 98 transmits only the raw measurements, converted signals, and/or corrected signals.

One potential difficulty that may be experienced with the on-skin sensor control unit 44 is a change in the transmission frequency of the transmitter 98 over time. To overcome this potential difficulty, the transmitter may include optional circuitry that can return the frequency of the transmitter 98 to the desired frequency or frequency band. One example of suitable circuitry is illustrated in FIG. 21 as a block diagram of an open loop modulation system 200. The open loop modulation system 200 includes a phase detector (PD) 210, a charge pump (CHGPM) 212, a loop filter (L.F.) 214, a voltage controlled oscillator (VCO) 216, and a divide by M circuit (+M) 218 to form the phase-locked loop 220.

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The analyte monitoring device 40 uses an open loop modulation system 200 for RF communication between the transmitter 98 and a receiver of, for example, the one or more receiver/display units 46, 48. This open loop modulation system 230 is designed to provide a high reliability RF link between a transmitter and its associated receiver. The system employs frequency modulation (FM), and locks the carrier center frequency using a conventional phase-locked loop (PLL) 220. In operation, the phase-locked loop 220 is opened prior to the modulation. During the modulation the phase-locked loop 220 remains open for as long as the center frequency of the transmitter is within the receiver's bandwidth. When the transmitter detects that the center frequency is going to move outside of the receiver bandwidth, the receiver is signaled to stand by while the center frequency is captured. Subsequent to the capture, the transmission will resume. This cycle of capturing the center frequency, opening the phase-locked loop 220, modulation, and recapturing the center frequency will repeat for as many cycles as required.

The loop control 240 detects the lock condition of the phase-locked loop 220 and is responsible for closing and opening the phase-locked loop 220. The totalizer 250 in conjunction with the loop control 240, detects the status of the center frequency. The modulation control 230 is responsible for generating the modulating signal. A transmit amplifier 260 is provided to ensure adequate transmit signal power. The reference frequency is generated from a very stable signal source (not shown), and is divided down by N through the divide by N block (+N) 270. Data and control signals are received by the open loop modulation system 200 via the DATA BUS 280, and the CONTROL BUS 290.

The operation of the open loop modulation system 200 begins with the phase-locked loop 220 in closed condition. When the lock condition is detected by the loop control 240, the phase-locked loop 220 is opened and the modulation control 230 begins generating the modulating signal. The totalizer 250 monitors the VCO frequency (divided by M), for programmed intervals. The monitored frequency is compared to a threshold programmed in the totalizer 250. This threshold corresponds to the 3 dB cut off frequencies of the receiver's intermediate frequency stage. When the monitored frequency approaches the thresholds, the loop control 240 is notified and a stand-by code is transmitted to the receiver and the phase-locked loop 220 is closed.

At this point the receiver is in the wait mode. The loop control 240 in the transmitter closes the phase-locked loop 220. Then, modulation control 230 is taken off line, the monitored value of the totalizer 250 is reset, and the phase-locked loop 220 is locked. When the loop control 240 detects a lock condition, the loop control 240 opens the phase-locked loop 220, the modulation control 230 is brought on line and the data transmission to the receiver will resume until the center frequency of the phase-locked loop 220 approaches the threshold values, at which point the cycle of transmitting the stand-by code begins. The +N 270 and +M 218 block set the frequency channel of the transmitter.

Accordingly, the open loop modulation system 200 provides a reliable low power FM data transmission for an analyte monitoring system. The open loop modulation system 200 provides a method of wide band frequency modulation, while the center frequency of the carrier is kept within receiver bandwidth. The effect of parasitic capacitors and inductors pulling the center frequency of the transmitter is corrected by the phase-locked loop 220. Further, the totalizer 250 and loop control 240 provide a new method of center frequency drift detection. Finally, the open loop modulation system 200 is easily implemented in CMOS process.

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The rate at which the transmitter 98 transmits data may be the same rate at which the sensor circuit 97 obtains signals and/or the processing circuit 109 provides data or signals to the transmitter 98. Alternatively, the transmitter 98 may transmit data at a slower rate. In this case, the transmitter 98 may transmit more than one datapoint in each transmission. Alternatively, only one datapoint may be sent with each data transmission, the remaining data not being transmitted. Typically, data is transmitted to the receiver/display unit 46, 48 at least every hour, preferably, at least every fifteen minutes, more preferably, at least every five minutes, and most preferably, at least every one minute. However, other data transmission rates may be used. In some embodiments, the processing circuit 109 and/or transmitter 98 are configured to process and/or transmit data at a faster rate when a condition is indicated, for example, a low level or high level of analyte or impending low or high level of analyte. In these embodiments, the accelerated data transmission rate is typically at least every five minutes and preferably at least every minute.

In addition to a transmitter 98, an optional receiver 99 may be included in the on-skin sensor control unit 44. In some cases, the transmitter 98 is a transceiver, operating as both a transmitter and a receiver. The receiver 99 may be used to receive calibration data for the sensor 42. The calibration data may be used by the processing circuit 109 to correct signals from the sensor 42. This calibration data may be transmitted by the receiver/display unit 46, 48 or from some other source such as a control unit in a doctor's office. In addition, the optional receiver 99 may be used to receive a signal from the receiver/display units 46, 48, as described above, to direct the transmitter 98, for example, to change frequencies or frequency bands, to activate or deactivate the optional alarm system 94 (as described below), and/or to direct the transmitter 98 to transmit at a higher rate.

Calibration data may be obtained in a variety of ways. For instance, the calibration data may simply be factory-determined calibration measurements which can be input into the on-skin sensor control unit 44 using the receiver 99 or may alternatively be stored in a calibration data storage unit 100 within the on-skin sensor control unit 44 itself (in which case a receiver 99 may not be needed). The calibration data storage unit 100 may be, for example, a readable or readable/writeable memory circuit.

Alternative or additional calibration data may be provided based on tests performed by a doctor or some other professional or by the patient himself. For example, it is common for diabetic individuals to determine their own blood glucose concentration using commercially available testing kits. The results of this test is input into the on-skin sensor control unit 44 either directly, if an appropriate input device (e.g., a keypad, an optical signal receiver, or a port for connection to a keypad or computer) is incorporated in the on-skin sensor control unit 44, or indirectly by inputting the calibration data into the receiver/display unit 46, 48 and transmitting the calibration data to the on-skin sensor control unit 44.

Other methods of independently determining analyte levels may also be used to obtain calibration data. This type of calibration data may supplant or supplement factory-determined calibration values.

In some embodiments of the invention, calibration data may be required at periodic intervals, for example, every eight hours, once a day, or once a week, to confirm that accurate analyte levels are being reported. Calibration may also be required each time a new sensor 42 is implanted or if the sensor exceeds a threshold minimum or maximum

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value or if the rate of change in the sensor signal exceeds a threshold value. In some cases, it may be necessary to wait a period of time after the implantation of the sensor 42 before calibrating to allow the sensor 42 to achieve equilibrium. In some embodiments, the sensor 42 is calibrated only after it has been inserted. In other embodiments, no calibration of the sensor 42 is needed.

The on-skin sensor control unit 44 and/or a receiver/display unit 46, 48 may include an auditory or visual indicator that calibration data is needed, based, for example, on a predetermined periodic time interval between calibrations or on the implantation of a new sensor 42. The on-skin sensor control unit 44 and/or receiver display/units 46, 48 may also include an auditory or visual indicator to remind the patient that information, such as analyte levels, reported by the analyte monitoring device 40, may not be accurate because a calibration of the sensor 42 has not been performed within the predetermined periodic time interval and/or after implantation of a new sensor 42.

The processing circuit 109 of the on-skin sensor control unit 44 and/or an analyzer 152 of the receiver/display unit 46, 48 may determine when calibration data is needed and if the calibration data is acceptable. The on-skin sensor control unit 44 may optionally be configured to not allow calibration or to reject a calibration point if, for example, 1) a temperature reading from the temperature probe indicates a temperature that is not within a predetermined acceptable range (e.g., 30 to 42° C. or 32 to 40° C.) or that is changing rapidly (for example, 0.2° C./minute, 0.5° C./minute, or 0.7° C./minute or greater); 2) two or more working electrodes 58 provide uncalibrated signals that are not within a predetermined range (e.g., within 10% or 20%) of each other; 3) the rate of change of the uncalibrated signal is above a threshold rate (e.g., 0.25 mg/dL per minute or 0.5 mg/dL per minute or greater); 4) the uncalibrated signal exceeds a threshold maximum value (e.g., 5, 10, 20, or 40 nA) or is below a threshold minimum value (e.g., 0.05, 0.2, 0.5, or 1 nA); 5) the calibrated signal exceeds a threshold maximum value (e.g., a signal corresponding to an analyte concentration of 200 mg/dL, 250 mg/dL, or 300 mg/dL) or is below a threshold minimum value (e.g., a signal corresponding to an analyte concentration of 50 mg/dL, 65 mg/dL, or 80 mg/dL); and/or 6) an insufficient amount of time has elapsed since implantation (e.g., 10 minutes or less, 20 minutes or less, or 30 minutes or less).

The processing circuit 109 or an analyzer 152 may also request another calibration point if the values determined using the sensor data before and after the latest calibration disagree by more than a threshold amount, indicating that the calibration may be incorrect or that the sensor characteristics have changed radically between calibrations. This additional calibration point may indicate the source of the difference.

The on-skin sensor control unit 44 may include an optional data storage unit 102 which may be used to hold data (e.g., measurements from the sensor or processed data) from the processing circuit 109 permanently or, more typically, temporarily. The data storage unit 102 may hold data so that the data can be used by the processing circuit 109 to analyze and/or predict trends in the analyte level, including, for example, the rate and/or acceleration of analyte level increase or decrease. The data storage unit 102 may also or alternatively be used to store data during periods in which a receiver/display unit 46, 48 is not within range. The data storage unit 102 may also be used to store data when the transmission rate of the data is slower than the acquisition rate of the data. For example, if the data acqui-

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sition rate is 10 points/min and the transmission is 2 transmissions/min, then one to five points of data could be sent in each transmission depending on the desired rate for processing datapoints. The data storage unit **102** typically includes a readable/writeable memory storage device and typically also includes the hardware and/or software to write to and/or read the memory storage device.

The on-skin sensor control unit **44** may include an optional alarm system **104** that, based on the data from the processing circuit **109**, warns the patient of a potentially detrimental condition of the analyte. For example, if glucose is the analyte, than the on-skin sensor control unit **44** may include an alarm system **104** that warns the patient of conditions such as hypoglycemia, hyperglycemia, impending hypoglycemia, and/or impending hyperglycemia. The alarm system **104** is triggered when the data from the processing circuit **109** reaches or exceeds a threshold value. Examples of threshold values for blood glucose levels are about 60, 70, or 80 mg/dL for hypoglycemia; about 70, 80, or 90 mg/dL for impending hypoglycemia; about 130, 150, 175, 200, 225, 250, or 275 mg/dL for impending hyperglycemia; and about 150, 175, 200, 225, 250, 275, or 300 mg/dL for hyperglycemia. The actual threshold values that are designed into the alarm system **104** may correspond to interstitial fluid glucose concentrations or electrode measurements (e.g., current values or voltage values obtained by conversion of current measurements) that correlate to the above-mentioned blood glucose levels. The analyte monitor device may be configured so that the threshold levels for these or any other conditions may be programmable by the patient and/or a medical professional.

A threshold value is exceeded if the datapoint has a value that is beyond the threshold value in a direction indicating a particular condition. For example, a datapoint which correlates to a glucose level of 200 mg/dL exceeds a threshold value for hyperglycemia of 180 mg/dL, because the datapoint indicates that the patient has entered a hyperglycemic state. As another example, a datapoint which correlates to a glucose level of 65 mg/dL exceeds a threshold value for hypoglycemia of 70 mg/dL because the datapoint indicates that the patient is hypoglycemic as defined by the threshold value. However, a datapoint which correlates to a glucose level of 75 mg/dL would not exceed the same threshold value for hypoglycemia because the datapoint does not indicate that particular condition as defined by the chosen threshold value.

An alarm may also be activated if the sensor readings indicate a value that is beyond a measurement range of the sensor **42**. For glucose, the physiologically relevant measurement range is typically about 50 to 250 mg/dL, preferably about 40–300 mg/dL and ideally 30–400 mg/dL, of glucose in the interstitial fluid.

The alarm system **104** may also, or alternatively, be activated when the rate of change or acceleration of the rate of change in analyte level increase or decrease reaches or exceeds a threshold rate or acceleration. For example, in the case of a subcutaneous glucose monitor, the alarm system might be activated if the rate of change in glucose concentration exceeds a threshold value which might indicate that a hyperglycemic or hypoglycemic condition is likely to occur.

The optional alarm system **104** may be configured to activate when a single data point meets or exceeds a particular threshold value. Alternatively, the alarm may be activated only when a predetermined number of datapoints spanning a predetermined amount of time meet or exceed the threshold value. As another alternative, the alarm may be

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activated only when the datapoints spanning a predetermined amount of time have an average value which meets or exceeds the threshold value. Each condition that can trigger an alarm may have a different alarm activation condition. In addition, the alarm activation condition may change depending on current conditions (e.g., an indication of impending hyperglycemia may alter the number of datapoints or the amount of time that is tested to determine hyperglycemia).

The alarm system **104** may contain one or more individual alarms. Each of the alarms may be individually activated to indicate one or more conditions of the analyte. The alarms may be, for example, auditory or visual. Other sensory-stimulating alarm systems may be used including alarm systems which heat, cool, vibrate, or produce a mild electrical shock when activated. In some embodiments, the alarms are auditory with a different tone, note, or volume indicating different conditions. For example, a high note might indicate hyperglycemia and a low note might indicate hypoglycemia. Visual alarms may use a difference in color, brightness, or position on the on-skin sensor control device **44** to indicate different conditions. In some embodiments, an auditory alarm system is configured so that the volume of the alarm increases over time until the alarm is deactivated.

In some embodiments, the alarm may be automatically deactivated after a predetermined time period. In other embodiments, the alarm may be configured to deactivate when the data no longer indicate that the condition which triggered the alarm exists. In these embodiments, the alarm may be deactivated when a single data point indicates that the condition no longer exists or, alternatively, the alarm may be deactivated only after a predetermined number of datapoints or an average of datapoints obtained over a given period of time indicate that the condition no longer exists.

In some embodiments, the alarm may be deactivated manually by the patient or another person in addition to or as an alternative to automatic deactivation. In these embodiments, a switch **101** is provided which when activated turns off the alarm. The switch **101** may be operatively engaged (or disengaged depending on the configuration of the switch) by, for example, operating an actuator on the on-skin sensor control unit **44** or the receiver/display unit **46**, **48**. In some cases, an actuator may be provided on two or more units **44**, **46**, **48**, any of which may be actuated to deactivate the alarm. If the switch **101** and/or actuator is provided on the receiver/display unit **46**, **48** then a signal may be transmitted from the receiver/display unit **46**, **48** to the receiver **98** on the on-skin sensor control unit **44** to deactivate the alarm.

A variety of switches **101** may be used including, for example, a mechanical switch, a reed switch, a Hall effect switch, a Gigantic Magnetic Ratio (GMR) switch (the resistance of the GMR switch is magnetic field dependent) and the like. Preferably, the actuator used to operatively engage (or disengage) the switch is placed on the on-skin sensor control unit **44** and configured so that no water can flow around the button and into the housing. One example of such a button is a flexible conducting strip that is completely covered by a flexible polymeric or plastic coating integral to the housing. In an open position the flexible conducting strip is bowed and bulges away from the housing. When depressed by the patient or another person, the flexible conducting strip is pushed directly toward a metal contact and completes the circuit to shut off the alarm.

For a reed or GMR switch, a piece of magnetic material, such as a permanent magnet or an electromagnet, in a flexible actuator that is bowed or bulges away from the housing **45** and the reed or GMR switch is used. The reed or



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GMR switch is activated (to deactivate the alarm) by depressing the flexible actuator bringing the magnetic material closer to the switch and causing an increase in the magnetic field within the switch.

In some embodiments of the invention, the analyte monitoring device **40** includes only an on-skin control unit **44** and a sensor **42**. In these embodiments, the processing circuit **109** of the on-skin sensor control unit **44** is able to determine a level of the analyte and activate an alarm system **104** if the analyte level exceeds a threshold. The on-skin control unit **44**, in these embodiments, has an alarm system **104** and may also include a display, such as those discussed below with respect to the receiver/display units **46, 48**. Preferably, the display is an LCD or LED display. The on-skin control unit **44** may not have a transmitter, unless, for example, it is desirable to transmit data, for example, to a control unit in a doctor's office.

The on-skin sensor control unit **44** may also include a reference voltage generator **101** to provide an absolute voltage or current for use in comparison to voltages or currents obtained from or used with the sensor **42**. An example of a suitable reference voltage generator is a band-gap reference voltage generator that uses, for example, a semiconductor material with a known band-gap. Preferably, the band-gap is temperature insensitive over the range of temperatures that the semiconductor material will experience during operation. Suitable semiconductor materials include gallium, silicon and silicates.

A bias current generator **105** may be provided to correctly bias solid-state electronic components. An oscillator **107** may be provided to produce a clock signal that is typically used with digital circuitry.

The on-skin sensor control unit **44** may also include a watchdog circuit **103** that tests the circuitry, particularly, any digital circuitry in the control unit **44** to determine if the circuitry is operating correctly. Non-limiting examples of watchdog circuit operations include: a) generation of a random number by the watchdog circuit, storage of the number in a memory location, writing the number to a register in the watchdog circuit, and recall of the number to compare for equality; b) checking the output of an analog circuit to determine if the output exceeds a predetermined dynamic range; c) checking the output of a timing circuit for a signal at an expected pulse interval. Other examples of functions of a watchdog circuit are known in the art. If the watchdog circuit detects an error that watchdog circuit may activate an alarm and/or shut down the device.

#### Receiver/Display Unit

One or more receiver/display units **46, 48** may be provided with the analyte monitoring device **40** for easy access to the data generated by the sensor **42** and may, in some embodiments, process the signals from the on-skin sensor control unit **44** to determine the concentration or level of analyte in the subcutaneous tissue. Small receiver/display units **46** may be carried by the patient. These units **46** may be palm-sized and/or may be adapted to fit on a belt or within a bag or purse that the patient carries. One embodiment of the small receiver/display unit **46** has the appearance of a pager, for example, so that the user is not identified as a person using a medical device. Such receiver/display units may optionally have one-way or two-way paging capabilities.

Large receiver/display units **48** may also be used. These larger units **48** may be designed to sit on a shelf or nightstand. The large receiver/display unit **48** may be used by parents to monitor their children while they sleep or to awaken patients during the night. In addition, the large

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receiver/display unit **48** may include a lamp, clock, or radio for convenience and/or for activation as an alarm. One or both types of receiver/display units **46, 48** may be used.

The receiver/display units **46, 48**, as illustrated in block form at FIG. **22**, typically include a receiver **150** to receive data from the on-skin sensor control unit **44**, an analyzer **152** to evaluate the data, a display **154** to provide information to the patient, and an alarm system **156** to warn the patient when a condition arises. The receiver/display units **46, 48** may also optionally include a data storage device **158**, a transmitter **160**, and/or an input device **162**. The receiver/display units **46, 48** may also include other components (not shown), such as a power supply (e.g., a battery and/or a power supply that can receive power from a wall outlet), a watchdog circuit, a bias current generator, and an oscillator. These additional components are similar to those described above for the on-skin sensor control unit **44**.

In one embodiment, a receiver/display unit **48** is a bedside unit for use by a patient at home. The bedside unit includes a receiver and one or more optional items, including, for example, a clock, a lamp, an auditory alarm, a telephone connection, and a radio. The bedside unit also has a display, preferably, with large numbers and/or letters that can be read across a room. The unit may be operable by plugging into an outlet and may optionally have a battery as backup. Typically, the bedside unit has a better antenna than a small palm-size unit, so the bedside unit's reception range is longer.

When an alarm is indicated, the bedside unit may activate, for example, the auditory alarm, the radio, the lamp, and/or initiate a telephone call. The alarm may be more intense than the alarm of a small palm-size unit to, for example, awaken or stimulate a patient who may be asleep, lethargic, or confused. Moreover, a loud alarm may alert a parent monitoring a diabetic child at night.

The bedside unit may have its own data analyzer and data storage. The data may be communicated from the on-skin sensor unit or another receiver/display unit, such as a palm-size or small receiver/display unit. Thus, at least one unit has all the relevant data so that the data can be downloaded and analyzed without significant gaps.

Optionally, the bedside unit has an interface or cradle into which a small receiver/display unit may be placed. The bedside unit may be capable of utilizing the data storage and analysis capabilities of the small receiver/display unit and/or receive data from the small receiver/display unit in this position. The bedside unit may also be capable of recharging a battery of the small receiver/display unit.

The receiver **150** typically is formed using known receiver and antenna circuitry and is often tuned or tunable to the frequency or frequency band of the transmitter **98** in the on-skin sensor control unit **44**. Typically, the receiver **150** is capable of receiving signals from a distance greater than the transmitting distance of the transmitter **98**. The small receiver/display unit **46** can typically receive a signal from an on-skin sensor control unit **44** that is up to 2 meters, preferably up to 5 meters, and more preferably up to 10 meters or more, away. A large receiver/display unit **48**, such as a bedside unit, can typically receive a signal from an on-skin sensor control unit **44** that is up to 5 meters distant, preferably up to 10 meters distant, and more preferably up to 20 meters distant or more.

In one embodiment, a repeater unit (not shown) is used to boost a signal from an on-skin sensor control unit **44** so that the signal can be received by a receiver/display unit **46, 48** that may be distant from the on-skin sensor control unit **44**. The repeater unit is typically independent of the on-skin



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sensor control unit **44**, but, in some cases, the repeater unit may be configured to attach to the on-skin sensor control unit **44**. Typically, the repeater unit includes a receiver for receiving the signals from the on-skin sensor control unit **44** and a transmitter for transmitting the received signals. Often the transmitter of the repeater unit is more powerful than the transmitter of the on-skin sensor control unit, although this is not necessary. The repeater unit may be used, for example, in a child's bedroom for transmitting a signal from an on-skin sensor control unit on the child to a receiver/display unit in the parent's bedroom for monitoring the child's analyte levels. Another exemplary use is in a hospital with a display/receiver unit at a nurse's station for monitoring on-skin sensor control unit(s) of patients.

The presence of other devices, including other on-skin sensor control units, may create noise or interference within the frequency band of the transmitter **98**. This may result in the generation of false data. To overcome this potential difficulty, the transmitter **98** may also transmit a code to indicate, for example, the beginning of a transmission and/or to identify, preferably using a unique identification code, the particular on-skin sensor control unit **44** in the event that there is more than one on-skin sensor control unit **44** or other transmission source within range of the receiver/display unit **46, 48**. The provision of an identification code with the data may reduce the likelihood that the receiver/display unit **46, 48** intercepts and interprets signals from other transmission sources, as well as preventing "crosstalk" with different on-skin sensor control units **44**. The identification code may be provided as a factory-set code stored in the sensor control unit **44**. Alternatively, the identification code may be randomly generated by an appropriate circuit in the sensor control unit **44** or the receiver/display unit **46, 48** (and transmitted to the sensor control unit **44**) or the identification code may be selected by the patient and communicated to the sensor control unit **44** via a transmitter or an input device coupled to the sensor control unit **44**.

Other methods may be used to eliminate "crosstalk" and to identify signals from the appropriate on-skin sensor control unit **44**. In some embodiments, the transmitter **98** may use encryption techniques to encrypt the datastream from the transmitter **98**. The receiver/display unit **46, 48** contains the key to decipher the encrypted data signal. The receiver/display unit **46, 48** then determines when false signals or "crosstalk" signals are received by evaluation of the signal after it has been deciphered. For example, the analyzer **152** in the one or more receiver/display units **46, 48** compares the data, such as current measurements or analyte levels, with expected measurements (e.g., an expected range of measurements corresponding to physiologically relevant analyte levels). Alternatively, an analyzer in the receiver/display units **46, 48** searches for an identification code in the decrypted data signal.

Another method to eliminate "crosstalk", which is typically used in conjunction with the identification code or encryption scheme, includes providing an optional mechanism in the on-skin sensor control unit **44** for changing transmission frequency or frequency bands upon determination that there is "crosstalk". This mechanism for changing the transmission frequency or frequency band may be initiated by the receiver/display unit automatically, upon detection of the possibility of cross-talk or interference, and/or by a patient manually. For automatic initiation, the receiver/display unit **46, 48** transmits a signal to the optional receiver **99** on the on-skin sensor control unit **44** to direct the transmitter **98** of the on-skin sensor control unit **44** to change frequency or frequency band.

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Manual initiation of the change in frequency or frequency band may be accomplished using, for example, an actuator (not shown) on the receiver/display unit **46, 48** and/or on the on-skin sensor control unit **44** which a patient operates to direct the transmitter **98** to change frequency or frequency band. The operation of a manually initiated change in transmission frequency or frequency band may include prompting the patient to initiate the change in frequency or frequency band by an audio or visual signal from the receiver/display unit **46, 48** and/or on-skin sensor control unit **44**.

Returning to the receiver **150**, the data received by the receiver **150** is then sent to an analyzer **152**. The analyzer **152** may have a variety of functions, similar to the processor circuit **109** of the on-skin sensor control unit **44**, including 1) modifying the signals from the sensor **42** using calibration data and/or measurements from the temperature probe **66**, 2) determining a level of an analyte in the interstitial fluid, 3) determining a level of an analyte in the bloodstream based on the sensor measurements in the interstitial fluid, 4) determining if the level, rate of change, and/or acceleration in the rate of change of the analyte exceeds or meets one or more threshold values, 5) activating an alarm system **156** and/or **94** if a threshold value is met or exceeded, 6) evaluating trends in the level of an analyte based on a series of sensor signals, 7) determine a dose of a medication, and 7) reduce noise or error contributions (e.g., through signal averaging or comparing readings from multiple electrodes). The analyzer **152** may be simple and perform only one or a small number of these functions or the analyzer **152** may perform all or most of these functions.

The output from the analyzer **152** is typically provided to a display **154**. A variety of displays **154** may be used including cathode ray tube displays (particularly for larger units), LED displays, or LCD displays. The display **154** may be monochromatic (e.g., black and white) or polychromatic (i.e., having a range of colors). The display **154** may contain symbols or other indicators that are activated under certain conditions (e.g., a particular symbol may become visible on the display when a condition, such as hyperglycemia, is indicated by signals from the sensor **42**). The display **154** may also contain more complex structures, such as LCD or LED alphanumeric structures, portions of which can be activated to produce a letter, number, or symbol. For example, the display **154** may include region **164** to display numerically the level of the analyte, as illustrated in FIG. **23**. In one embodiment, the display **154** also provides a message to the patient to direct the patient in an action. Such messages may include, for example, "Eat Sugar", if the patient is hypoglycemic, or "Take Insulin", if the patient is hyperglycemic.

One example of a receiver/display unit **46, 48** is illustrated in FIG. **23**. The display **154** of this particular receiver/display unit **46, 48** includes a portion **164** which displays the level of the analyte, for example, the blood glucose concentration, as determined by the processing circuit **109** and/or the analyzer **152** using signals from the sensor **42**. The display also includes various indicators **166** which may be activated under certain conditions. For example, the indicator **168** of a glucose monitoring device may be activated if the patient is hyperglycemic. Other indicators may be activated in the cases of hypoglycemia (**170**), impending hyperglycemia (**172**), impending hypoglycemia (**174**), a malfunction, an error condition, or when a calibration sample is needed (**176**). In some embodiments, color coded indicators may be used. Alternatively, the portion **164** which displays the blood glucose concentration may also include a

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composite indicator **180** (see FIG. 24), portions of which may be appropriately activated to indicate any of the conditions described above.

The display **154** may also be capable of displaying a graph **178** of the analyte level over a period of time, as illustrated in FIG. 24. Examples of other graphs that may be useful include graphs of the rate of change or acceleration in the rate of change of the analyte level over time. In some embodiments, the receiver/display unit is configured so that the patient may choose the particular display (e.g., blood glucose concentration or graph of concentration versus time) that the patient wishes to view. The patient may choose the desired display mode by pushing a button or the like, for example, on an optional input device **162**.

The receiver/display units **46, 48** also typically include an alarm system **156**. The options for configuration of the alarm system **156** are similar to those for the alarm system **104** of the on-skin sensor control unit **44**. For example, if glucose is the analyte, then the on-skin sensor control unit **44** may include an alarm system **156** that warns the patient of conditions such as hypoglycemia, hyperglycemia, impending hypoglycemia, and/or impending hyperglycemia. The alarm system **156** is triggered when the data from the analyzer **152** reaches or exceeds a threshold value. The threshold values may correspond to interstitial fluid glucose concentrations or sensor signals (e.g., current or converted voltage values) which correlate to the above-mentioned blood glucose levels.

The alarm system **156** may also, or alternatively, be activated when the rate or acceleration of an increase or decrease in analyte level reaches or exceeds a threshold value. For example, in the case of a subcutaneous glucose monitor, the alarm system **156** might be activated if the rate of change in glucose concentration exceeds a threshold value which might indicate that a hyperglycemic or hypoglycemic condition is likely to occur.

The alarm system **156** may be configured to activate when a single data point meets or exceeds a particular threshold value. Alternatively, the alarm may be activated only when a predetermined number of datapoints spanning a predetermined amount of time meet or exceed the threshold value. As another alternative, the alarm may be activated only when the datapoints spanning a predetermined amount of time have an average value which meets or exceeds the threshold value. Each condition that can trigger an alarm may have a different alarm activation condition. In addition, the alarm activation condition may change depending on current conditions (e.g., an indication of impending hyperglycemia may alter the number of datapoints or the amount of time that is tested to determine hyperglycemia).

The alarm system **156** may contain one or more individual alarms. Each of the alarms may be individually activated to indicate one or more conditions of the analyte. The alarms may be, for example, auditory or visual. Other sensory-stimulating alarm systems may be used including alarm systems **156** that direct the on-skin sensor control unit **44** to heat, cool, vibrate, or produce a mild electrical shock. In some embodiments, the alarms are auditory with a different tone, note, or volume indicating different conditions. For example, a high note might indicate hyperglycemia and a low note might indicate hypoglycemia. Visual alarms may also use a difference in color or brightness to indicate different conditions. In some embodiments, an auditory alarm system might be configured so that the volume of the alarm increases over time until the alarm is deactivated.

In some embodiments, the alarms may be automatically deactivated after a predetermined time period. In other

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embodiments, the alarms may be configured to deactivate when the data no longer indicate that the condition which triggered the alarm exists. In these embodiments, the alarms may be deactivated when a single data point indicates that the condition no longer exists or, alternatively, the alarm may be deactivated only after a predetermined number of datapoints or an average of datapoints obtained over a given period of time indicate that the condition no longer exists.

In yet other embodiments, the alarm may be deactivated manually by the patient or another person in addition to or as an alternative to automatic deactivation. In these embodiments, a switch is provided which when activated turns off the alarm. The switch may be operatively engaged (or disengaged depending on the configuration of the switch) by, for example, pushing a button on the receiver/display unit **46, 48**. One configuration of the alarm system **156** has automatic deactivation after a period of time for alarms that indicate an impending condition (e.g., impending hypoglycemia or hyperglycemia) and manual deactivation of alarms which indicate a current condition (e.g., hypoglycemia or hyperglycemia).

The receiver/display units **46, 48** may also include a number of optional items. One item is a data storage unit **158**. The data storage unit **158** may be desirable to store data for use if the analyzer **152** is configured to determine trends in the analyte level. The data storage unit **158** may also be useful to store data that may be downloaded to another receiver/display unit, such as a large display unit **48**. Alternatively, the data may be downloaded to a computer or other data storage device in a patient's home, at a doctor's office, etc. for evaluation of trends in analyte levels. A port (not shown) may be provided on the receiver/display unit **46, 48** through which the stored data may be transferred or the data may be transferred using an optional transmitter **160**. The data storage unit **158** may also be activated to store data when directed by the patient via, for example, the optional input device **162**. The data storage unit **158** may also be configured to store data upon occurrence of a particular event, such as a hyperglycemic or hypoglycemic episode, exercise, eating, etc. The storage unit **158** may also store event markers with the data of the particular event. These event markers may be generated either automatically by the display/receiver unit **46, 48** or through input by the patient.

The receiver/display unit **46, 48** may also include an optional transmitter **160** which can be used to transmit 1) calibration information, 2) a signal to direct the transmitter **98** of the on-skin sensor control unit **44** to change transmission frequency or frequency bands, and/or 3) a signal to activate an alarm system **104** on the on-skin sensor control unit **44**, all of which are described above. The transmitter **160** typically operates in a different frequency band than the transmitter **98** of the on-skin sensor control unit **44** to avoid cross-talk between the transmitters **98, 160**. Methods may be used to reduce cross-talk and the reception of false signals, as described above in connection with the transmitter **100** of the on-skin sensor control unit **44**. In some embodiments, the transmitter **160** is only used to transmit signals to the sensor control unit **44** and has a range of less than one foot, and preferably less than six inches. This then requires the patient or another person to hold the receiver/display unit **46** near the sensor control unit **44** during transmission of data, for example, during the transmission of calibration information. Transmissions may also be performed using methods other than rf transmission, including optical or wire transmission.

In addition, in some embodiments of the invention, the transmitter **160** may be configured to transmit data to

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another receiver/display unit **46, 48** or some other receiver. For example, a small receiver/display unit **46** may transmit data to a large receiver/display unit **48**, as illustrated in FIG. 1. As another example, a receiver/display unit **46, 48** may transmit data to a computer in the patient's home or at a doctor's office. Moreover, the transmitter **160** or a separate transmitter may direct a transmission to another unit or to a telephone or other communications device that alerts a doctor or other individual when an alarm is activated and/or if, after a predetermined time period, an activated alarm has not been deactivated, suggesting that the patient may require assistance. In some embodiments, the receiver/display unit is capable of one-way or two-way paging and/or is coupled to a telephone line to send and/or receive messages from another, such as a health professional monitoring the patient.

Another optional component for the receiver/display unit **46, 48** is an input device **162**, such as a keypad or keyboard. The input device **162** may allow numeric or alphanumeric input. The input device **162** may also include buttons, keys, or the like which initiate functions of and/or provide input to the analyte monitoring device **40**. Such functions may include initiating a data transfer, manually changing the transmission frequency or frequency band of the transmitter **98**, deactivating an alarm system **104, 156**, inputting calibration data, and/or indicating events to activate storage of data representative of the event.

Another embodiment of the input device **162** is a touch screen display. The touch screen display may be incorporated into the display **154** or may be a separate display. The touch screen display is activated when the patient touches the screen at a position indicated by a "soft button" which corresponds to a desired function. Touch screen displays are well known.

In addition, the analyte monitoring device **40** may include password protection to prevent the unauthorized transmission of data to a terminal or the unauthorized changing of settings for the device **40**. A patient may be prompted by the display **154** to input the password using the input device **152** whenever a password-protected function is initiated.

Another function that may be activated by the input device **162** is a deactivation mode. The deactivation mode may indicate that the receiver/display unit **46, 48** should no longer display a portion or all of the data. In some embodiments, activation of the deactivation mode may even deactivate the alarm systems **104, 156**. Preferably, the patient is prompted to confirm this particular action. During the deactivation mode, the processing circuit **109** and/or analyzer **152** may stop processing data or they may continue to process data and not report it for display and may optionally store the data for later retrieval.

Alternatively, a sleep mode may be entered if the input device **162** has not been activated for a predetermined period of time. This period of time may be adjustable by the patient or another individual. In this sleep mode, the processing circuit **109** and/or analyzer **152** typically continue to obtain measurements and process data, however, the display is not activated. The sleep mode may be deactivated by actions, such as activating the input device **162**. The current analyte reading or other desired information may then be displayed.

In one embodiment, a receiver/display unit **46** initiates an audible or visual alarm when the unit **46** has not received a transmission from the on-skin sensor control unit within a predetermined amount of time. The alarm typically continues until the patient responds and/or a transmission is received. This can, for example, remind a patient if the receiver/display unit **46** is inadvertently left behind.

In another embodiment, the receiver/display unit **46, 48** is integrated with a calibration unit (not shown). For example,

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the receiver/display unit **46, 48** may, for example, include a conventional blood glucose monitor. Another useful calibration device utilizing electrochemical detection of analyte concentration is described in U.S. patent application Ser. No. 08/795,767, incorporated herein by reference. Other devices may be used including those that operate using, for example, electrochemical and calorimetric blood glucose assays, assays of interstitial or dermal fluid, and/or non-invasive optical assays. When a calibration of the implanted sensor is needed, the patient uses the integrated in vitro monitor to generate a reading. The reading may then, for example, automatically be sent by the transmitter **160** of the receiver/display unit **46, 48** to calibrate the sensor **42**.

#### Integration with a Drug Administration System

FIG. **25** illustrates a block diagram of a sensor-based drug delivery system **250** according to the present invention. The system may provide a drug to counteract the high or low level of the analyte in response to the signals from one or more sensors **252**. Alternatively, the system monitors the drug concentration to ensure that the drug remains within a desired therapeutic range. The drug delivery system includes one or more (and preferably two or more) subcutaneously implanted sensors **252**, an on-skin sensor control unit **254**, a receiver/display unit **256**, a data storage and controller module **258**, and a drug administration system **260**. In some cases, the receiver/display unit **256**, data storage and controller module **258**, and drug administration system **260** may be integrated in a single unit. The sensor-based drug delivery system **250** uses data from the one or more sensors **252** to provide necessary input for a control algorithm/mechanism in the data storage and controller module **252** to adjust the administration of drugs. As an example, a glucose sensor could be used to control and adjust the administration of insulin.

In FIG. **25**, sensor **252** produces signals correlated to the level of the drug or analyte in the patient. The level of the analyte will depend on the amount of drug delivered by the drug administration system. A processor **262** in the on-skin sensor control unit **254**, as illustrated in FIG. **25**, or in the receiver/display unit **256** determines the level of the analyte, and possibly other information, such as the rate or acceleration of the rate in the increase or decrease in analyte level. This information is then transmitted to the data storage and controller module **252** using a transmitter **264** in the on-skin sensor control unit **254**, as illustrated in FIG. **25**, or a non-integrated receiver/display unit **256**.

If the drug delivery system **250** has two or more sensors **252**, the data storage and controller module **258** may verify that the data from the two or more sensors **252** agrees within predetermined parameters before accepting the data as valid. This data may then be processed by the data storage and controller module **258**, optionally with previously obtained data, to determine a drug administration protocol. The drug administration protocol is then executed using the drug administration system **260**, which may be an internal or external infusion pump, syringe injector, transdermal delivery system (e.g., a patch containing the drug placed on the skin), or inhalation system. Alternatively, the drug storage and controller module **258** may provide a the drug administration protocol so that the patient or another person may provide the drug to the patient according to the profile.

In one embodiment of the invention, the data storage and controller module **258** is trainable. For example, the data storage and controller module **258** may store glucose readings over a predetermined period of time, e.g., several weeks. When an episode of hypoglycemia or hyperglycemia is encountered, the relevant history leading to such event



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may be analyzed to determine any patterns which might improve the system's ability to predict future episodes. Subsequent data might be compared to the known patterns to predict hypoglycemia or hyperglycemia and deliver the drug accordingly. In another embodiment, the analysis of trends is performed by an external system or by the processing circuit **109** in the on-skin sensor control unit **254** or the analyzer **152** in the receiver/display unit **256** and the trends are incorporated in the data storage and controller **258**.

In one embodiment, the data storage and controller module **258**, processing circuit **109**, and/or analyzer **152** utilizes patient-specific data from multiple episodes to predict a patient's response to future episodes. The multiple episodes used in the prediction are typically responses to a same or similar external or internal stimulus. Examples of stimuli include periods of hypoglycemia or hyperglycemia (or corresponding conditions for analytes other than glucose), treatment of a condition, drug delivery (e.g., insulin for glucose), food intake, exercise, fasting, change in body temperature, elevated or lowered body temperature (e.g., fever), and diseases, viruses, infections, and the like. By analyzing multiple episodes, the data storage and controller module **258**, processing circuit **109**, and/or analyzer **152** can predict the course of a future episode and provide, for example, a drug administration protocol or administer a drug based on this analysis. An input device (not shown) may be used by the patient or another person to indicate when a particular episode is occurring so that, for example, the data storage and controller module **258**, processing circuit **109**, and/or analyzer **152** can tag the data as resulting from a particular episode, for use in further analyses.

In addition, the drug delivery system **250** may be capable of providing on-going drug sensitivity feedback. For example, the data from the sensor **252** obtained during the administration of the drug by the drug administration system **260** may provide data about the individual patient's response to the drug which can then be used to modify the current drug administration protocol accordingly, both immediately and in the future. An example of desirable data that can be extracted for each patient includes the patient's characteristic time constant for response to drug administration (e.g., how rapidly the glucose concentration falls when a known bolus of insulin is administered). Another example is the patient's response to administration of various amounts of a drug (e.g., a patient's drug sensitivity curve). The same information may be stored by the drug storage and controller module and then used to determine trends in the patient's drug response, which may be used in developing subsequent drug administration protocols, thereby personalizing the drug administration process for the needs of the patient.

The present invention should not be considered limited to the particular examples described above, but rather should be understood to cover all aspects of the invention as fairly set out in the attached claims. Various modifications, equivalent processes, as well as numerous structures to which the present invention may be applicable will be readily apparent to those of skill in the art to which the present invention is directed upon review of the instant specification. The claims are intended to cover such modifications and devices.

We claim:

1. A sensor assembly to monitor an analyte, the sensor assembly comprising:

- a transcutaneous electrochemical sensor comprising non-leachable, analyte-responsive enzyme; and
- a sensor control unit adapted for placement on skin and adapted for receiving a portion of the transcutaneous

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electrochemical sensor, the sensor control unit comprising a rf transmitter that is configured and arranged to intermittently and repeatedly transmit data related to analyte-dependent signals generated by the electrochemical sensor.

2. The sensor assembly of claim **1**, wherein the sensor control unit comprises at least one conductive contact and the transcutaneous electrochemical sensor comprises at least one working electrode and at least one contact pad coupled to the at least one working electrode, the at least one contact pad being disposed on a portion of the electrochemical sensor extending out of the skin, wherein the at least one conductive contact is configured and arranged to contact the at least one contact pads.

3. The sensor assembly of claim **1**, wherein the sensor control unit is adapted to receive a portion of the transcutaneous electrochemical sensor extending out of the skin, the transcutaneous electrochemical sensor comprising a planar substrate.

4. The sensor assembly of claim **1**, wherein the sensor control unit is adapted for placement on the skin over an insertion site of the transcutaneous electrochemical sensor.

5. The sensor assembly of claim **1**, wherein the sensor control unit is water resistant.

6. The sensor assembly of claim **1**, wherein the sensor control unit further comprises a battery.

7. The sensor assembly of claim **1**, wherein the sensor control unit further comprises an alarm to indicate at least one of hypoglycemia, impending hypoglycemia, hyperglycemia, and impending hyperglycemia.

8. The sensor assembly of claim **1**, wherein the sensor control unit further comprises a rf receiver.

9. The sensor assembly of claim **1**, wherein the sensor control unit further comprises a processing circuit for determining a level of the analyte from a signal generated by the transcutaneous electrochemical sensor.

10. The sensor assembly of claim **1**, wherein the analyte is glucose and the non-leachable, analyte-responsive enzyme is a non-leachable, glucose-responsive enzyme.

11. An analyte monitoring system to monitor a level of an analyte, the analyte monitoring system, comprising:

- a transcutaneous electrochemical sensor comprising non-leachable, analyte-responsive enzyme;
- a sensor control unit adapted for placement on skin and adapted for receiving a portion of the transcutaneous electrochemical sensor, the sensor control unit comprising a rf transmitter that is configured and arranged to intermittently and repeatedly transmit data related to analyte-dependent signals generated by the electrochemical sensor; and
- a display unit comprising a rf receiver to receive the data from the sensor control unit and a display coupled to the rf receiver for displaying an indication of a level of the analyte.

12. The analyte monitoring system of claim **11**, wherein the display unit further comprises a rf transmitter.

13. The analyte monitoring system of claim **12**, wherein the sensor control unit further comprises a rf receiver disposed in the housing.

14. The analyte monitoring system of claim **11**, wherein the display unit further comprises an input device coupled to the display.

15. The analyte monitoring system of claim **11**, further comprising a calibrator for providing a calibration value to at least one of the display unit and the sensor control unit.

16. The analyte monitoring system of claim **15**, wherein the calibrator comprises a part of the display unit.



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17. The analyte monitoring system of claim 11, wherein the display unit is portable.

18. The analyte monitoring system of claim 11, further comprising a secondary display unit having a power cord for connecting to an electrical outlet, a receiver for receiving data transmitted by the transmitter, and a display coupled to the receiver for displaying the level of the analyte.

19. The analyte monitoring system of claim 11, wherein the display unit further comprises at least one of a lamp, a radio, a clock, an interface to a computer, or a battery backup system.

20. The analyte monitoring system of claim 11, wherein the display unit further comprises a pager receiver or an interface to a telephone system to receive messages.

21. The analyte monitoring system of claim 11, wherein the display unit comprises a pager transmitter or an interface to a telephone system to send messages.

22. The analyte monitoring system of claim 21, wherein the pager transmitter or the interface to the telephone system is activated when at least one of hypoglycemia, impending hypoglycemia, hyperglycemia, or impending hyperglycemia is indicated.

23. The analyte monitoring system of claim 11, further comprising a processing circuit in the display unit, the processing circuit being configured to analyze patient-specific data from multiple episodes to predict a patient's response to future episodes.

24. The analyte monitoring system of claim 11, wherein the analyte monitoring system further comprises a drug administration system which dispenses a drug based on a level of the analyte.

25. The analyte monitoring system of claim 11, wherein the analyte is glucose and the non-leachable, analyte-responsive enzyme is a non-leachable, glucose-responsive enzyme.

26. A glucose monitoring system, comprising:

a transcutaneous electrochemical glucose sensor;  
a sensor control unit adapted for placement on skin and adapted for receiving a portion of the transcutaneous electrochemical glucose sensor, the sensor control unit comprising a rf transmitter that is configured and arranged to intermittently and repeatedly transmit data related to glucose-dependent signals generated by the electrochemical glucose sensor; and

a display unit comprising a rf receiver to receive the data transmitted by the transmitter and a display to display an indication of glucose concentration, wherein the display unit is configured and arranged to determine an insulin administration protocol based on the data.

27. The glucose monitoring system of claim 26, further comprising a processing circuit in the display unit, the processing circuit being configured to analyze patient-specific data from multiple episodes to predict a patient's response to future episodes.

28. The glucose monitoring system of claim 27, wherein the patient-specific data comprises a response to a treatment.

29. The glucose monitoring system of claim 28, wherein the treatment is an administration of insulin.

30. The glucose monitoring system of claim 27, wherein the display unit further comprises an input device for indicating when a treatment is administered.

31. The glucose monitoring system of claim 27, wherein the processing circuit is configured to determine a drug administration protocol in response to the patient-specific data.

32. The glucose monitoring system of claim 27, wherein the patient-specific data is a dosage dependence of a response to a drug.

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33. The glucose monitoring system of claim 27, wherein the display unit further comprises an input device for indicating when food has been ingested.

34. The glucose monitoring system of claim 33, where the input device is configured for indicating an approximate caloric content of the food.

35. The glucose monitoring system of claim 26, further comprising a temperature measurement device to correct data obtained from the sensor.

36. The glucose monitoring system of claim 26, wherein the glucose monitoring system further comprises a drug administration system which dispenses a drug based on a level of glucose.

37. The glucose monitoring system of claim 36, wherein the drug administration system comprises a receiver for receiving data from at least one of the sensor control unit or display unit to direct dispensing of the drug.

38. The glucose monitoring system of claim 36, wherein the drug administration system comprises at least one of a needle, syringe, pump, catheter, inhaler, or transdermal patch to administer the drug.

39. A glucose monitoring system, comprising:

a transcutaneous electrochemical glucose sensor;

a sensor control unit adapted for placement on skin and adapted for receiving a portion of the transcutaneous electrochemical glucose sensor, the sensor control unit comprising a rf transmitter that is configured and arranged to intermittently and repeatedly transmit data related to glucose-dependent signals generated by the electrochemical glucose sensor; and

a display unit comprising a rf receiver to receive the data transmitted by the transmitter and a display to display an indication of glucose concentration, wherein the display unit is configured and arranged to analyze a plurality of glucose-dependent signals related to a particular type of episode to predict a patient's response to future episodes of the type.

40. The glucose monitoring system of claim 39, wherein the episode comprises a response to a treatment.

41. The glucose monitoring system of claim 40, wherein the treatment is an administration of insulin.

42. The glucose monitoring system of claim 40, wherein the display unit further comprises an input device for indicating when a treatment is administered.

43. The glucose monitoring system of claim 39, wherein the display unit is configured to determine a drug administration protocol in response to the episode.

44. The glucose monitoring system of claim 39, wherein the episode is a dosage dependence of a response to a drug.

45. The glucose monitoring system of claim 39, wherein the display unit further comprises an input device for indicating when food has been ingested.

46. The glucose monitoring system of claim 45, where the input device is configured for indicating an approximate caloric content of the food.

47. A method of monitoring glucose, the method comprising:

determining a glucose concentration of a patient using a glucose sensor;

collecting data including the glucose concentration in a personal display unit comprising a transmitter and a receiver;

transmitting the data to a health professional;

transmitting a message, in response to the data, from the health professional to the personal display unit; and displaying the message from the health professional on the personal display unit.

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48. The method of claim 47, further comprising inserting transcutaneously the glucose sensor prior to determining the glucose concentration.

49. The method of claim 47, wherein the glucose sensor comprises an electrochemical glucose sensor.

50. The method of claim 47, further comprising coupling the glucose sensor to a sensor control unit, wherein the sensor control unit is configured and arranged for disposition on skin of the patient, the sensor control unit comprising a rf transmitter, and transmitting a rf transmission signal from the sensor control unit to the personal display unit based on at least one signal generated by the glucose sensor.

51. The method of claim 50, wherein determining a glucose concentration comprises determining a glucose concentration using the personal display unit.

52. The method of claim 47, further comprising activating an alarm in the personal display unit, wherein the alarm is configured for activating under one or more of the following conditions: hypoglycemia, impending hypoglycemia, hyperglycemia, and impending hyperglycemia.

53. The method of claim 47, wherein transmitting the data comprises transmitting the data to the health professional at regular intervals.

54. The method of claim 47, wherein transmitting the data comprises transmitting the data to the health professional

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when a specific condition is present, wherein the specific condition is one or more of the following: hypoglycemia, impending hypoglycemia, hyperglycemia, and impending hyperglycemia.

55. The method of claim 47, wherein transmitting the data comprises transmitting the data using a pager or an interface to a telephone system.

56. A sensor assembly to monitor an analyte, the sensor assembly comprising:

a transcutaneous electrochemical sensor; and

a sensor control unit adapted for placement on skin, the sensor control unit comprising a power source and a rf transmitter that is configured and arranged to intermittently and repeatedly transmit data related to analyte-dependent signals generated by the electrochemical sensor, wherein the sensor control unit is configured and arranged to both deliver power to the transcutaneous electrochemical sensor and receive the analyte-dependent signals from the transcutaneous electrochemical sensor by inductive coupling between the sensor control unit and the transcutaneous electrochemical sensor.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 6,565,509 B1  
DATED : May 20, 2003  
INVENTOR(S) : Say et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 56,

Line 36, "trancutaneous" should read -- transcutaneous --

Column 58,

Lines 3 and 52, "injested" should read -- ingested --

Column 59,

Line 2, "trancutaneously" should read -- transcutaneously --

Column 60,

Line 19, "trancutaneous" should read -- transcutaneous --

Signed and Sealed this

Twelfth Day of August, 2003

A handwritten signature in black ink, appearing to read "James E. Rogan", with a long horizontal flourish extending from the bottom of the signature.

JAMES E. ROGAN  
*Director of the United States Patent and Trademark Office*